REMARKS

This paper is filed in Response to the Office Action mailed March 23, 2010. Claims 27 to 43 and 48 to 51 are pending. Claims 52 to 54 have been added. Accordingly, upon entry of this paper, claims 27 to 32, 34 to 43 and 48 to 54 are under consideration.

Applicants respectfully request an interview with the Examiner of sufficient duration to discuss all grounds for rejection that may remain upon consideration of this paper and the accompanying documents submitted herewith.

The Amendments to the Specification

The specification has been amended to correct informalities. In particular, the specification has been amended to correct the heavy chain variable region (V_H) sequence of SAM-6.10 antibody (aka SAM-6 antibody) produced by the SAM-6.10 producing hybridoma cell line, namely Arg-Pro, and to correct certain terms, at page 9, lines 1-5. The amendment is supported, for example, at page 13, lines 8-96, which discloses the SAM-6.10 antibody (aka SAM-6 antibody) producing hybridoma, which antibody has the heavy chain variable region (V_H) sequence (see, also, page 4 of the Sequence Listing). As evidenced by the specific reference to the SAM-6.10 antibody producing hybridoma, and the accompanying Statement under 37 C.F.R. §1.804(b) executed by Dr. Frank Hensel, Applicants had possession of the hybridoma that produces SAM-6.10 antibody and the SAM-6.10 antibody heavy and light chain variable region sequences at the time the application was filed. The specification has also been amended to insert the deposit information for the SAM-6.10 antibody producing hybridoma, namely, DSM ACC2903. The Description for Figure 5 at page 22 has been renumbered to delete reference to incorrectly referenced Figure 9.

Thus, the amendments were made to address informalities or are supported by the specification, and no new matter has been added. Consequently, entry thereof is respectfully requested.

The Claim Amendments

The claim amendments are supported throughout the specification or were made to address informalities. In particular, the amendment to claim 27 to recite that "the heavy chain (V_H) variable region sequence comprises an amino acid sequence at least 80% identical to the amino acid sequence of SEQ ID:3," is supported, for example, by originally filed claim 17, and at page 9, second paragraph. The amendment to claim 31 to recite "V_H" is supported,

for example, by originally filed claim 5. The amendment to claim 43 to correct the sequence of heavy chain variable region (V_H) is supported, for example, at page 13, lines, 8-9, which discloses SAM-6.10 (aka as SAM-6) antibody producing hybridoma, and the accompanying executed Statement under 37 C.F.R. §1.804(b). Thus, as the claim amendments are supported throughout the originally filed specification or were made to address an informality, no new matter has been added and entry thereof is respectfully requested.

The New Claims

Claims 52 to 54 are supported throughout the specification. In particular, claims 52 to 54 are supported, for example, by originally filed claims 1 and 17, at page 7, second and third paragraphs, and at page 8, third paragraph, to page 9, second paragraph. Thus, as claims 52 to 54 are supported throughout the originally filed specification, no new matter has been added and entry thereof is respectfully requested.

The Substitute Sequence Listing

A Substitute Sequence Listing is submitted herewith to correct errors in the sequences, namely SEQ ID NOs:3 and 4. In particular, the correct SEQ ID NO:3 amino acid sequence has, at position 39, Gln, position 106, Arg, and position 107, Pro. The substitute sequence listing does not add new matter as the correction at position 39 of SEQ ID NO:3 is of an obvious error (translation error, the codon CAG, as shown in SEQ ID NO:4, encodes Gln, and not Glu). Support for the corrections at amino acid positions 106 and 107 of SEQ ID NO:3, and the corresponding codons for those positions, is as set forth above for the amendments to the specification. Accompanying executed Statements under 37 C.F.R. §§1.825(a) and (b) that no new matter has been added are submitted concurrently herewith. Thus, the Substitute Sequence Listing does not add new matter and entry thereof is respectfully requested.

Exhibit B

Attached for the Examiner's consideration are binding studies demonstrating that SAM-6.10 (aka SAM-6) ScFv, and a heavy chain variable region sequence alone (VH alone, SEQ ID NO:3), without a light chain variable region sequence, bind to target. In particular, ELISA analysis revealed that ScFv SAM-6, and a heavy chain variable region sequence, SAM-6 VH alone (SEQ ID NO:3) binds to apolipoprotein B100, a component of LDL.

Accordingly, Applicants respectfully request consideration of the accompanying binding data.

The Priority Claim, Inventorship, and the Oath/Declaration

Applicants have re-submitted the executed documents to correct inventorship, namely the Statements under 37 C.F.R. §1.48(a)(2) by Philip Vollmers and Heinz Vollmers (professionally aka Heinz Peter Vollmers), the Declaration and Power of Attorney, and the Assignee's consent to change Inventorship under 37 C.F.R. §1.48(a)(5) all with improved legibility, which were all originally filed October 21, 2009 with an accompanying Petition to Correct Inventorship under 35 U.S.C. §116 and 37 C.F.R. §1.48(a)(1). As discussed in the record, inventorship of International application no. PCT/DE2004/002503 was corrected to Heinz Peter Vollmers, as indicated by Form PCT/IB/306 issued during the international phase. This application was filed listing an incorrect inventor Philip Vollmers. Applicants respectfully request that the inventorship be corrected in view of the resubmitted fully executed documents. Accordingly, inventorship of this application is in the name of Heinz Peter Vollmers, which therefore properly claims priority to International application no. PCT/DE2004/002503.

Information Disclosure Statements

Applicants thank the Examiner for the information concerning German language references submitted in the IDS. Applicants have previously submitted English language equivalents in an IDS for consideration. Applicants therefore believe that English language equivalents for all references in the German language have been considered.

Objections to the Specification

The Examiner has indicated that the Descriptions of Figures 1, 2, 4 and 5 allegedly are unclear and certain deficiencies remain.

The specification has been amended to delete reference to Figure 9, at page 21, and now recites only Figure 5. In view of the amendment, the ground for objection is moot.

In terms of Figures 1 and 2 having no y-axis label, which allegedly "makes evaluation of the data therein confusing," and that "units of what is being measured is necessary," Applicants respectfully point out that the y-axis label, and the data in Figures 1 and 2, are understandable in view of the description of the two respective figures in the specification at

pages 19-20. In particular, in the paragraph bridging pages 19-20, the description states that "Figure 1 shows the measurement of oxLDL in dependence on the incubation time," and that "in the experiment, LDL....was oxidized for 3 and 15 h," and that "the amount of oxidized LDL increases with increasing incubation time." The y-axis of both Figures 1 and 2 show increasing values of "0.2," "0.4," etc. Consequently, obviously the y-axis reflects the LDL oxidation, which obviously increases with increasing incubation time as reflected by the longer bars. Thus, clearly the y-axis indicates the amount of LDL measured and units are not necessary to understand that more oxididized LDL is present (again as reflected by the longer bars) with increasing oxidation time from 0, to 3 to 15 h. Consequently, the data represented in Figure 1 is clear to one of skill in the art.

In terms of the assertion that "Figure 2 cannot be evaluated because there is no distinction between the kontrolle and SAM-6 as the bars are both open," at page 20, second paragraph, the description states that "Figure 2 shows the proof of binding of SAM-6 to oxLDL," and that "the result shows that the more LDL that is present in its oxidized form, the more strongly the antibody SAM-6 according to the invention binds," which is indicated by longer bars at each respective time point. At page 20, second paragraph, the description also states that "the ELISA plate was precoated with LDL fractions oxidized to different degrees," which as stated in the Figure 1 description is indicated by the 0, 3 and 15 h time points along the x-axis and the longer bars reflecting increased LDL oxidation. Consequently, obviously one of skill in the art based upon the foregoing description understands that the longer bars at each successive time point in Figure 2 reflect SAM-6 binding (i.e., "the more LDL that is present in its oxidized form, the more strongly the antibody SAM-6 according to the invention binds"), and the shorter bars reflect control (i.e., Kontrolle). Consequently, the data represented in Figure 2 is clear to one of skill in the art.

In terms of the description for Figure 4 implying that there should be two panels, and there is only one panel, which shows the SAM-6 treated mouse macrophages. The IgM control antibody is not shown in Figure 4, due to an inadvertent omission of a second panel. However, the description at pages 20-21 again makes clear what the Sudan III staining studies show, namely SAM-6 binding to fat in macrophages. Furthermore, the description of Figure 5 which relates to the same type of macrophage studies makes it clear that lipid accumulation in cells can be detected by SAM-6. Consequently, in view of the description the results intended to be shown in Figure 4 are clear. Furthermore, Figure 4 is not essential to an understanding of the invention or for evaluating patentability of the claims.

In view of the foregoing amendment and remarks, the description of the data intended to be represented by the Figures is sufficiently clear to one of skill in the art. Consequently, Applicants respectfully request that the objection to the specification be withdrawn.

I. REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH, ENABLEMENT

The rejection of claims 27 to 32, 34 to 43 and 48 to 51 under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement is respectfully traversed. The grounds for rejection are set forth in the Office Action, pages 6-16.

Applicants respectfully point out that claims 27 to 32, 34 to 43 and 48 to 51 require both the light (V_L) and heavy (V_H) chain variable region sequences. Thus, given that the claims require both light chain (V_L) variable region and heavy chain (V_H) variable region sequences, all 6 CDRs are present. Furthermore, new claims 52 to 54 recite the predicted CDRs of light (V_L) and/or heavy (V_H) chain variable region sequences, which confer antigen binding specificity. Thus, given that claims 52 to 54 require sequences that confer antigen binding specificity, clearly antibodies within the scope of the claims can be readily identified without undue experimentation.

As previously pointed out in the record, in view of the guidance in the specification and the high level of knowledge and skill in the art at the time of the invention relevant to antibody structure and function, variants that bind LDL or oxLDL could be produced and identified using routine methods disclosed in the specification or that were known in the art at the time of the invention without undue experimentation. Importantly, such methods do not require detailed structure-function understanding of antibodies since the antigen, LDL or oxLDL, to which the antibodies bind is known and variant antibodies could be readily produced and screened for binding without undue experimentation. Consequently, it is not essential that the skilled artisan "predict" antibody variants or fragments that bind to LDL or oxLDL because introducing minor changes into antibody sequences and identifying those that bind to LDL or oxLDL was routine at the time of the invention.

By way of example, the specification discloses antibody heavy and/or light chain variable region (SEQ ID NOs:3 or1) sequences that confer binding to LDL or oxLDL, and the predicted locations of the CDRs. Consequently, in view of the specification already has a functional antibody, SAM-6.1, the skilled artisan knows sequences that confer binding to LDL or oxLDL, and the predicted sequences of all CDRs of the sequences (see, pages 8-9, of the specification). The skilled artisan therefore has a "blueprint" to start with, namely SEQ

ID NOs:3 and 1 and the predicted locations of the CDRs, in making variant antibodies, and also has extensive knowledge concerning antibody structures that correlate with function, as discussed at length in the prior Office Action and disclosed in the specification (page 8, second paragraph). In view of the totality of this knowledge, one of skill in the art would merely introduce selected changes to SEQ ID NOs:1 or 3, using structure function knowledge and the location of the predicted CDRs, and then verify which antibodies bind to LDL or oxLDL, for example. Such a methodology of introducing changes into a heavy or light chain variable region sequences of an antibody known to bind to a given target, here LDL or oxLDL, where substantial knowledge concerning antibody structure and function as well as the location of the predicted CDRs was clearly well within the skill in the art at the time of the invention and would not require undue experimentation.

Further in regard to antibody binding, antibodies typically bind to proteins due their strong immunogenicity, and it is well understood in the art that there are proteins shared among vLDL, IDL, LDL and oxLDL. Such proteins include apolipoproteins, such as Apoprotein B (apoB). Apo B is the major protein in all lipoproteins, except high density lipoprotein (HDL).

Exhibit B submitted herewith includes data indicating that an ScFv comprising SEQ ID NO:1 and SEQ ID NO:3, light and heavy chain variable region sequences respectively, bind to apoB100, a component of LDL and oxLDL, but not HDL. Furthermore, Exhibit B includes data indicating SAM-6 heavy chain variable region sequence (VH) alone (SEQ ID NO:3) without a light chain variable region sequence binds to apoB100. In brief, ScFv with both VH and VL chains (SEQ ID NO:3 and SEQ ID NO:1), and variable region heavy chain (SEQ ID NO:3) without light chain, were analyzed for binding to apoB100, compared to an irrelevant IgM and other (negative) controls. The data revealed that ScFv (SEQ ID NO:1 and SEQ ID NO:3), and variable region heavy chain alone (SEQ ID NO:3), bind to apoB100. The data in Exhibit B confirms that identifying antibodies by binding to LDL or oxLDL would not present any particular difficulty since apoB100 is consistently present in LDL and oxLDL and, as such, would not require undue experimentation. The data in Exhibit B also confirms that binding to apoB100 is predominantly conferred by heavy chain variable region (SEQ ID NO:3), as a light chain is not required for binding.

Turning to the grounds for rejection due to purported differences with the facts in *In re Wands*, Applicants appreciate that the technology has advanced considerably between 1981 and when the priority application was filed in 2003. However, the fact is that screening

for antibodies that bind to a given target, here LDL or oxLDL, which among them there are sequence variations, is the very essence of the facts in *In re Wands*. As far back as 1981 in *Wands* one of skill in the art could readily identify antibodies that bind to a given target and without undue experimentation without any need to "predict" with certainty the effect of any particular variation or modification. As with the claims under consideration, antibody variants that bind to LDL or oxLDL can be identified using a routine binding assay without undue experimentation without any need to "predict" with certainty the effect of any particular variation or modification. The factual analogy with *Wands* applies to the subject claims because, again all that is required in order to make and identify antibodies and functional fragments within the scope of the claims is to produce a variant (using well known genetic techniques, for example), and ascertain binding to LDL or oxLDL, which as discussed above and in the record can be further confirmed by competition binding with LDL or oxLDL in the presence of SAM-6. Such routine assays, known in the art at the time of the invention, do not require particular knowledge of amino acids amenable to substitution, addition or deletion, or particular types of LDL or oxLDL. Consequently, the facts in *Wands* are highly analogous to the claims under consideration, and given the guidance in the specification, and particularly the high level and considerable advances in the knowledge and skill in the antibody art in 2003 as compared to 1981, clearly making and identifying variant antibodies and fragments within the scope of the claims would not require undue experimentation.

Previously submitted Exhibit A (Boder *et al.*, Proc. Nat'l Acad. Sci. USA 97:10701 (2000)), which report the directed evolution of scFv fragments, and generation of a large number of Fv sequences with improved binding affinity compared to non-mutagenized antibody, corroborate that variant antibodies that bind to LDL or oxLDL could be produced at the time of the invention without undue experimentation. In terms of the Patent Office's assertion at page 16 that one of skill in the art "would be required to test numerous and indefinite numbers of antigens as not all HDL and LDL is the same" in order to identify an antigen to which the antibodies bind, Applicants point out that the claimed antibodies and fragments bind to LDL or oxLDL, not HDL. Thus, it is unclear to Applicants what the meaning of this statement is in terms of "as not all HDL and LDL is the same." If the intended point was that differences between types of LDLs would make it difficult to identify antibodies that bind (due to possible differences in antigens?), there is no evidence that whatever differences, if any, there may be between LDLs and/or oxLDLs, that such

differences would result in undue experimentation in identifying antibodies that bind to LDL or oxLDL that have the requisite sequence identity. Indeed, the point is moot in view of the data submitted herewith (Exhibit B) indicating that SAM-6 binds to apoB100, which confirms that differences in LDLs or oxLDLs would not result in any additional difficulty in identifying antibodies that bind to LDL or oxLDL, since apoB100 is consistently present in LDL and oxLDL.

In short, all that is required of one of skill in the art to produce antibody variants is, starting with SEQ ID NOs:1 and 3 as a blueprint, produce a limited number of SEQ 1D NOs:1 and/or 3 variants with the benefit of substantial antibody structure and function knowledge and location of predicted CDRs, and verify which variants bind to LDL or oxLDL using a routine assay. To confirm binding to LDL or oxLDL, competition binding between a variant antibody to LDL or oxLDL in the presence of SAM-6 antibody can be performed, if desired.

In sum, in view of the guidance in the specification and the substantial knowledge and skill in the art at the time of the invention, the skilled artisan could readily produce and identify antibody variants and functional fragments based upon SEQ ID NO:1 and 3 without undue experimentation. Consequently, claims 27 to 32, 34 to 43 and 48 to 54 are adequately enabled under 35 U.S.C. §112, first paragraph, and Applicants respectfully request withdrawal of the rejection.

II. REJECTIONS UNDER 35 U.S.C. §102

The rejection of claims 27 to 43 and 48 to 51 under 35 U.S.C. §102(b), as allegedly anticipated by EP 1531162A1 (Vollmers et al.) is respectfully traversed. The grounds for rejection are set forth in the Office Action, pages 16-17.

Claim 33 has been cancelled without prejudice. Thus, the rejection of claim 33 is moot.

As discussed above and in the record, a Petition to correct the inventorship of the application under 37 C.F.R. §1.48(a)(2), to list Heinz Peter Vollmers was filed on October 21, 2009. Legible copies of the previously filed documents in support of the Petition to correct the inventorship have been submitted herewith. Accordingly, grant of the Petition is respectfully requested, at such time this national phase application properly claims priority to International application no. PCT/DE2004/002503, filed November 12, 2004. As such, EP 1531162A1, published May 18, 2005, is not available as prior art under 35 U.S.C. §102 against claims 27 to 32, 34 to 43 and 48 to 54.

The rejection of claims 27 to 43 and 48 to 51 under 35 U.S.C. §102(f), allegedly due to Applicants not inventing the claimed subject matter is respectfully traversed. The grounds for rejection are set forth in the Office Action, page 17.

Claim 33 has been cancelled without prejudice. Thus, the rejection of claim 33 is moot.

As discussed above, a Petition to correct the inventorship of the application under 37 C.F.R. §1.48(a)(2), to list Heinz Peter Vollmers was filed on October 21, 2009. Legible copies of the previously filed documents in support of the Petition to correct the inventorship have been submitted herewith. Accordingly, grant of the Petition is respectfully requested, at at such time this national phase application properly claims priority to International application no. PCT/DE2004/002503. Consequently, Applicant invented the claimed subject matter and therefore, the rejection under 35 U.S.C. §102(f) must be withdrawn.

CONCLUSION

In summary, for the reasons set forth herein, Applicants maintain that claims 27 to 32, 34 to 43 and 48 to 54 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (858) 509-4065. Please charge any fees associated with the submission of this paper to Deposit Account Number 033975. The Commissioner for Patents is also authorized to credit any over payments to the above-referenced Deposit Account.

Respectfully submitted,

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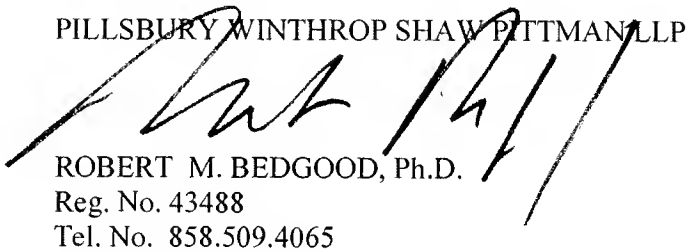

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